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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/981,087	05/27/1998	MICHAEL J. ELMORE	1498-133	7733

7590 10/28/2002

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EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
1647	29

DATE MAILED: 10/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/981,087	ELMORE ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *5-19,21,25,26,28 and 30-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *5-19, 21, 25-26, 28 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: Notice of Sequence Non-compliance.

Application No.: 08/981087

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: Figure 3 See Action

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 11-5-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/981,087 is acceptable and a CPA has been established. An action on the CPA follows.

Sequence Compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. " 131 and 132.

In particular it is noted that Figure 3 lists a nucleic acid sequence which is greater than 10 nucleotides in length. The Brief description of the drawings should be amended to reference the sequence by an appropriate SEQ ID NO.

Election/Restriction

3. Claims 5-19, 21, 25-26, 28 and 30-33 are pending and under examination.

Claim Objections

4. Claims 7, 8 and 26 are provisionally objected to under 37 CFR 1.75 as being substantial duplicates. Applicant is advised that should one of claims 7-8 or 26 be found allowable, the others will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In particular, each claim appears to recite fusion polypeptides where one element comprises a sequence from the group consisting of SEQ ID NO's:1-4. The second element of the claims appears to be a polypeptide that facilitates or enhances purification of the fusion protein/composition. The only noted difference in the claims is that claims 7-8 are specified to be a polypeptide composition whereas claim 26 is specified as being an isolated fusion protein. As the composition comprises only the fusion protein and the fusion protein is a composition of matter, the claims appear to be substantial duplicates. Claim 7 appears to be either a fusion protein or a composition of protein(s). Clarification of the difference in scope is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12, 17, 19, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for improved fertility upon vaccination

with a pharmaceutical preparation comprising SEQ ID NO:1, does not reasonably provide enablement for a vaccine, or pharmaceutical preparation comprising a smaller fragment of the protective seequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

In particular it is noted that the disclosure of a full-length peptide sequences does not lead the skilled artisan to specific epitopes which are protective to animals, even when protective antibodies which correspond to known peptide fragments are known, see in particular Sexton et al., J. of Immunol., 152(4):1861-72, 1994. The specification fails to delineate any smaller portion other than amino acids 848-1278 of SEQ ID NO:17-50 which are protective to animals against neurotoxin challenge and thus in the absence of further guidance the skilled artisan would be forced into further undue experimentation to define smaller protective epitopes which still retain protective capacity.

Further, with respect to this recitation, the skilled artisan recognizes that even in short peptides that single amino acid exchanges can eliminate antibody stimulation, recognition and binding, in addition to peptide function in an unpredictable manner, see in particular Choh et al., PNAS 77(6):3211-14, 1980. The specification fails to teach any smaller portion which is protective and fails to teach other analogues or analogue

fragments which could comprise the fusion peptides while retaining protective activity as recognized for the full length peptide of SEQ ID NO:1.

With respect to applicants recitation of a pharmaceutical composition and vaccine composition it is noted that the peptide of SEQ ID NO:1 retains protective properties, however as set forth above no other protective epitope or fragments have been delineated by applicants specification or claims. Thus, the skilled artisan has no guidance or assurance that the alternative fragments SEQ ID NO:2-4 could be used as a vaccine or pharmaceutical which provides benefit to the host. Thus, these recitations require further undue experimentation of behalf of the artisan to determine those alternative portions which describes a fragment capable of mediating any vaccine or pharmaceutical effect as claimed.

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation to make and use the claimed invention.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 recites the fusion protein of claim 26 wherein said C. botulinum amino acid sequence consists of SEQ ID NO:1. There is improper antecedent basis for "said C.botulinum amino acid sequence" within claim 26.

Claim 30 recites improper Markush language rendering the components to be selected indefinite to the artisan. It is suggeeested that applicants use selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claim 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Campbell et al., J. Clin. Microbiol., 31, 2255-2262, 1993 and Genbank Accession No. X70821.

Campbell et al., teach gene probes for identification of botulinal neurotoxin gene and specific identification of neurotoxin types B, E and F. The sequences include BoNT F, strain Langeland, see in particular Figure 3, sequence (2). SEQ ID NO:2 represents BoNT F, Langeland, amino acids 848-991 which are encoded by the nucleic acid sequence of Campbell represented by Accession No. X70821, see in particular p. 2257,

2nd column, 2nd paragrah. Thus, the reference teachings anticipate the claimed invention.

11. Claims 5 and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Elmore et al., Genbank Accession No. L35496, 23 August 1994.

Elmore et al., teach the BoNT Fgene nucleic and amino acid sequences. The amino acids are 100% identical with instant SEQ ID NO's:1-4 and the nucleic acids encode SEQ ID NO's 1-4. Thus, the reference teachings anticipate the claimed invention.

12. Claims 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Wadsworth et al., Biochem J., 268:123-128, 1990.

Wadsworth et al., teach large-scale purification and characterization of botulinum type F neurotoxin, strain Langeland. Although the reference is silent as to the particular amino acids, the isolated peptides necessarily and inherently comprise the amino acids of SEQ ID NO's:1-4 as they are the same. The polypeptide exists as a dimer with heavy and light chain subunits linked via disulfide bonds, see in particular column 1, p. 123. The reference also teaches a composition comprising urea for purification, see in particular p. p. 124, column 1, Purification of the heavy subunit of BoNT F. Additionally, the reference teaches purification and binding of I125 labeled toxin in a composition with rat brain synaptosomes, see in particular p. 124, columns 1-2.

13. Claims 5, 7, 12 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Hatheway et al., Applied and Environmental Microbiol., 31(2):234-242, 1976.

Hatheway et al., teach purification and characterization of botulinum type F neurotoxin via immunogenicity studies. Although the reference is silent as to the particular amino acids, the isolated peptides necessarily and inherently comprise the amino acids of SEQ ID NO's:1-4 as they are the same peptide isolated from clostridum botulinum. The reference teaches vaccine compositions comprising Holt's aluminum phosphate adjuvant and injection into guinea pigs. The toxin produced an anti-toxin response as indicated via isolation of sera antitoxin antibodies and protection to guinea pigs upon challenge, see in particular Figures 3-5 and Table 6 and immunogenicity testing, p. 236. Purification of the toxin is eased in compositions with DEAE-cellulose, see in patticular p. 235. Thus, the reference teachings anticipate the claimed invention.

Claim Rejections 35 USC 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 8-11, 14-17, 19, 21, 25, 26, and 30-31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell et al., J. Clin. Microbiol., 31, 2255-2262, 1993, Genbank Accession No. X70821, 1993, Elmore et al., Genbank Accession No. L35496, 23 August 1994, Wadsworth et al., Biochem J., 268:123-128, 1990 Hatheway et al., Applied and Environmental Microbiol., 31(2):234-242, 1976 and Kink et al., US 5,736,139.

Campbell, Elmore, Wadsworth and Hatheway teach as set forth above but do not teach polypeptide fusion proteins with the sequences of SEQ ID NO's:1-4 and with a peptide purification moiety that facilitates binding or purification, in particular where in the fusion binds an affinity column as in claims 8-11.

Kink teaches fusion proteins and peptide moieties capable of binding affinity chromatography columns for the purpose of aiding purification, see in particular columns 9-10, including maltose binding protein fusions, polyhistidine tag fusions and thioredoxin protein fusions.

As claimed in claims 14-18, 25, 26, and 30, the fusions may be prepared using recombinant DNA strategies with cleavage and elution upon addition of substrate maltose, see in particular columns 9-10, and Example 11, columns 52-56 as similarly disclosed in the specification, i.e., MBP fusions are the exemplary embodiments of the specification and are similarly isolated and purified using affinity chromatography. Kink

teaches the recombinant production via DNA of MBP fusion proteins. As set forth above the MBP, HIS or thioredoxin moieties are purification moieties which can bind an affinity chromatography column, see in particular columns 9-10, also Example 25.

As claimed in claim 19, and 21 the fusion proteins can be used as pharmaceutical compositions in the protection against botulinum/difficile toxin, see in particular Example 26-27 in a composition that comprises pHisBot or pMBot with in PBS containing Maltose with Gerbu adjuvant. The peptide of claim 26 is recombinantly produced as the artisan does not recognize botulinum toxin naturally produced with a purification moiety. Thus, the proteins recombinant production in combination with the procedures for its purification results in a composition which is free of contamination by other clostridial proteins as claimed in claim 31. As further evidence it is noted that the immune response generated via aministration of a mammal host, is specific for the purified toxins, see in particular Example 31. Thus Kink et al., teaches a method of producing antibodies in a mammal against botulinum toxin comprising administration of fusion protein compositions as in claim 33.

Thus, based on the Campbell, Elmore, Wadsworth and Hatheway's cumulative reference teachings of the nucleic and amino acid sequences of SEQ ID NO's:1-4, stimulation of antibody responses and protection via administration of clostridial botulinum neurotoxin type F pharmaceutical vaccine compositions and the superior method of providing recombinant fusion protein vaccines as provided in Kink, it would have been prima facie obvious for the artisan to modify the produce recombinant fusion constructs of Kink with the clostridial sequences to achieve production of purified

proteins for stimulatin an antibody response and providing protection against clostridum botulinum type F. One of skill in the art would have been motivated to make such modification knowing that the F antigen was protective in mammals and knowing that the Kink fusion procedure provides for the production of large quantities of purified and pharmaceutically compatible compositions. One of skill in the art would have expected success knowing the high skill in the art of recombinant peptide production. Thus, the cumulative reference teachings render the claimed invention obvious to the artisan.

Status of Claims

16. No claims are allowed.

17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
October 21, 2002

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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